

REMARKS

I. STATUS OF CLAIMS

Claims 45-76 are pending. No claim is amended herein.

II. REJECTION UNDER 35 U.S.C. § 103

A. Claims 45-59 and 63-76

Claims 45-59 and 63-76 are rejected under 35 U.S.C. § 103(a) over BRYAN GRIFFITHS & DENIS LOOBY, *Scale-Up of Suspension and Anchorage-Dependent Animal Cells*, in 75 METHODS IN MOLECULAR BIOLOGY: BASIC CELL CULTURE PROTOCOLS 59, 59-75 (Jeffrey W. Pollard & John M. Walker eds., 2d ed. 1997) ("Griffiths"). Office Action at p. 2. Applicant respectfully disagrees and traverses the rejection for the following reasons.

The Examiner bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. M.P.E.P. § 2142. In the present § 103 rejection, the Examiner is relying on the TSM rationale to support her conclusion of obviousness. See Office Action at p. 4. Under this rationale, the Examiner has the burden to at least demonstrate (1) a finding that there is some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; and (2) a finding that there was a reasonable expectation of success to make the proposed modification. See M.P.E.P. § 2143(G). Moreover, to establish a *prima facie* case of obviousness, the Examiner has the burden of establishing that the prior art references teach or suggest all the claim limitations. See *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Applicant respectfully submits that the Examiner has not met her

burden. Thus, the Examiner has failed to establish a *prima facie* case of obviousness over the cited references for at least the following reasons.

1. Griffiths fails to teach or suggest a repeated discontinuous process as claimed

Griffiths describes two approaches to scale-up: “The first [approach] is volumetric -- a simple increase in volume while retaining the same cell density or process intensity. See Griffiths at p. 60, lines 3-4. The second method described in Griffiths is to increase the cell density/unit vol 10-100-fold by means of medium perfusion techniques.” See *id.* at 4-6. Griffiths further teaches that scaling up “can be achieved by increasing the culture volume, and increasing the microcarrier concentration from the suggested 3-15 g/L.” See *id.* at p. 71, lines 15-17. Thus, the scale-up approaches described in Griffiths teach that the cell culture as a whole, not merely a portion of the cells, is transferred to a larger scale cultivation device.

In contrast, in the repeated discontinuous process claimed in independent claims 45 and 64, the cultured cells are split into two parts, wherein a first part of the cultured cells is transferred to be used for the preparation of at least one production batch (a culture of cells which is employed for the production of at least one virus), and the remaining part of the cultured cells (the second part) is used as a seed for the preparation of at least one subsequent preproduction batch. Griffiths fails to teach or suggest this type of repeated discontinuous process. Indeed, the Examiner even acknowledges this deficiency in Griffiths. Office Action at p. 3 (“Griffith et al. . . . do not explicitly state the harvested cells are split into at least two portions, wherein a portion of the cells are replated as a seed for a subsequent ‘preproduction batch,’ and a second

portion of the cells are transferred and used as a 'production batch' specifically for the production of biological products, which Applicants are calling a 'repeated discontinuous process'.).

Moreover, dividing the cell culture into a first part and a second part is not an inherent aspect of passaging as described in Griffiths. A "passage step" is defined in Applicant's specification as:

. . . a sequence of activities in the propagation and production of cells comprising at least the transfer of a suitable amount of cells and of a suitable amount of culturing medium into a production vessel, the incubation of the vessel at conditions suitable for the growing a propagation of the cells during a time sufficient for effective growing and propagation of the cells during a time sufficient for effective growing and propagation of the cells.

Applicant's specification at p. 3, lines 12-16. Based on this definition it is clear that "passaging of cells" involves transferring a number of cells from an existing vessel into a new vessel and is not the same as dividing the cells into two parts as in independent claims 45 and 64.

In the recent appeal in the present application, the Examiner asserted that "Griffiths' use of the term 'passaging' as meaning 'wherein 'passaging' involves splitting the culture and re-seeding and culturing at least one portion of the split culture.'" Decision on Appeal dated January 31, 2011, at p. 5. The Board of Patent Appeals and Interferences disagreed with the Examiner's assertion, stating that "Griffiths did not explicitly explain 'passaging' in that way, nor do we see evidence that 'passaging' was implicitly intended in that way." *See id.*

2. Deficiencies of the cited references cannot be remedied by the Office's general conclusions about what is "basic knowledge" or "common sense."

The Examiner acknowledges that:

Griffiths et al differ from the instant invention in that, while they disclose harvesting and passaging the cells of their 'preproduction batch', they do not explicitly state the harvested cells are split into at least two portions, wherein a first portion of the cells are replated as a seed for a subsequent 'preproduction batch,' and a second portion of the cells are transferred and used as a 'production batch' specifically for the production of biological products, which Applicants are calling a 'repeated discontinuous process.'

Office Action at p. 3. However, the Examiner asserts that "replating a portion of cells as a seed for subsequent 'preproduction batches', and transferring a second (larger) portion of cells for use as a 'production batch' for production of biological products produced by the cells (i.e. performing a repeated discontinuous process), would have been ***routinely performed by one of ordinary skill in the art.***" *Id.* (emphasis added). Applicant respectfully disagrees.

Since the claimed "repeated discontinuous process" is not taught by Griffiths, which the Examiner admits, the Examiner relies on "common sense" or "common knowledge" about what would have been routinely performed by one of ordinary skill in the art to support the obviousness rejection over Griffith. It is never appropriate to rely solely on "common knowledge" in the art without evidentiary support in the record, as the ***principal evidence*** upon which a rejection was based. M.P.E.P. § 2144.03; see also *In re Zurko*, 258 F.3d 1379, 1385, 59 U.S.P.Q.2d 1693, 1697 (emphasis added) ("[T]he Board cannot simply reach conclusions based on its own understanding or experience-or on its assessment of what would be basic knowledge or common sense.

Rather, the Board must point to some concrete evidence in the record in support of these findings."). Here, the Examiner admits that Griffiths does not teach the claimed "repeated discontinuous process," but then alleges that it would be routinely performed by one of ordinary skill in the art without pointing to any support for this allegation. As key facts relied on by the Examiner are not substantiated in documented evidence, the conclusion of obviousness cannot stand.

3. The Examiner failed to establish that Griffiths teach production batches having different passage numbers or teach "the passage number of each production batch is between master cell bank and extended cell bank"

Independent claim 45 recites that "the cells of the at least one first production batch in c) have a different passage number than the cells of the at least one subsequent production batch in e). In addition, claim 45 recites that "the passage number of each production batch is between master cell bank and extended cell bank, and the passage number ensures that the characteristics of the cells obey regulatory restrictions." Independent claim 64 includes similar language. Griffiths does not teach or suggest that a biological may be produced from production batches made according to the claimed invention in which those production batches have different passage numbers. On the contrary, conventional practice shows the production of a biological occurs in production batches all having the same passage number, e.g., serial production. See, e.g., U.S. Patent No. 4,664,912 to Wiktor et al. ("Wiktor") at col. 2, lines 68-69; see *also* Applicant's specification at page 1, lines 15-20 and p. 4, lines 26-34. In addition, Griffiths fails to teach or suggest that the passage number of each production batch is between master cell and extended cell bank. Further, the

validation and characterization of the extended cell bank, e.g., as in claims 63 and 76, guarantees that all passage numbers can safely be used for production without any further analytical efforts.

Moreover, Applicant would like to point out that the claim element “the passage number of each production batch is between master cell bank and extended cell bank” does not merely define a time period. In classical serial production, as described in Griffiths, the number of doubling of cells derived from the manufacturers working cell bank at the moment of harvest is known up front within certain limits. See Applicant’s specification at p. 4, lines 15-16. A maximum allowable generation number is set to the production system at the onset. *Id.* at lines 16-17. In contrast, in the claimed method, a bioreactor (manufacturer’s working cell bank) is fed with cells from the master cell bank. The cells from the working cell bank are propagated to a specific and characterized passage number for an extended cell bank. See *id.* at lines 19-20. Once the extended cell bank is fully characterized it allows one to produce the biological product with cells at any passage number between master cell bank and extended cell bank since it may be assumed that the cells have not changed. See *id.* at lines 29-32. As a result, tests on the manufacturer’s working cell bank can be limited to sterility testing, which is a particular advantage of the claimed invention. See *id.* at lines 32-33.

4. It would not have been obvious to simply apply the protocols of Griffiths to scaling-up cultures of MDCK cells for the production of viruses

The Examiner asserts that:

Furthermore though Griffith et al is non-specific with regards to the type of anchorage-dependent cell as well as the biological product being produced, it is submitted that the

teachings of Griffith et al are intended to be general, and thus are applicable to any well-known anchorage-dependent cell line which is capable of producing a desired biological product. . . . Therefore it would have been obvious at the time the invention was made to split and passage MDCK cells, per the repeated discontinuous culture process discussed above for the production of viruses, thereby meeting the limitations of claims 45-58 & 64-74.

Office Action at p. 6. Applicants respectfully disagree.

There are technical difficulties, *e.g.*, homogeneity problems, associated with scaling-up anchorage-dependent cells, *e.g.*, MDCK cells. Griffiths even recognizes these difficulties. See pages 59-60 and 65-66. In addition, other references in the pertinent art, for example, WO 97/37000 to Gröner et al. ("Gröner"), discuss the problems associated with scaling up of anchorage-dependent cells. Gröner at page 3, line 18 to page 4, lines 16. To address these problems, the process in Gröner converts anchorage-dependent cells to cells that grow in suspension to enable better scaling up. See claim 1, page 4, lines 19-24, page 5, lines 18-26, and Example 1. Thus, contrary to the Examiner's assertions, it would not have been obvious at the time the invention was made to simply apply the protocols of Griffiths to scaling-up cultures of MDCK cells for the production of viruses.

5. The proportion of cell culture to be transferred in each step is not a result effective variable

The Examiner admits that "the modified method of Griffith et al still differs from the method of instant claim 48 in that there are no teaching as to the specific proportion of the cell culture to be transferred in each step." Office Action at p. 7. The Examiner, however, asserts that "the difference between the proportions of the total cell culture allotted for production of biological product and for use as a subsequent preproduction

batch would have been routinely optimized by one having ordinary skill in the art.” *Id.*
Applicants respectfully disagree.

According to *In re Aller*, it would be obvious to optimize general conditions of a claim that are disclosed in the prior art. See 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). However, Griffiths fails to teach or suggest all the elements of Applicant’s claim 48, which the Examiner admits. See Office Action at p. 7 (“The modified method of Griffith et al still differs from the method of instant claim 48 in that there are no teachings as to the specific proportion of the cell culture to be transferred in each step”). Thus, modifying the proportions of cells disclosed in Griffiths especially the proportions of the cells used for at least one production batch and the cells used for at least one subsequent preproduction batch, cannot justifiably be considered merely determining optimum or workable ranges as in *In re Aller*. For at least these reasons, claim 48 is patentable over Griffiths.

For at least the foregoing reasons, the invention as claimed in independent claims 45 and 64 and the claims that depend therefrom would not have been obvious.

B. Claims 45-76

Claims 45-76 are rejected under 35 U.S.C. § 103(a) over U.S. Patent No. 4,664,912 to Wiktor et al. (“Wiktor”) in view of Griffiths, and further in view of Shimizu et al., “Improved Performance with Multiple Fermentors for Repeated Batch Cultivation for Non-Growth-Associated Products, Biotechnology & Bioengineering, Vol. 27, pp. 743-755 (1985) (“Shimizu”). Office Action at p. 8. Applicant respectfully disagrees and traverses the rejection for the following reasons.

As discussed above, to establish a *prima facie* case of obviousness, the Examiner has the burden of establishing that the prior art references teach or suggest all the claim limitations. See *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (CCPA 1974). Applicant respectfully submits that the Examiner has not met her burden. Thus, the Examiner has failed to establish a *prima facie* case of obviousness over the cited references for at least the following reasons.

1. The techniques used for culturing VERO cells are not equally applicable to MDCK cells

The Examiner asserts that the method of Wiktor is comparable to the method of the instant claims. However, the Examiner acknowledges that Wiktor “differs from the method the method of the instant claims in that (1) they are directed to production of a virus from VERO cells, whereas the instant claims are limited to production of a virus from MDCK cells” *Id.* at p. 9.

With regard to (1) the type of cells, the Examiner asserts that “it is submitted that both VERO cells and MDCK cells were notoriously well known at the time the invention made, are both anchorage-dependent animal cells, and were both well recognized as suitable cell types for production of viruses.” Office Action at p. 9. Therefore, the Examiner asserts that “[f]or purposes of this rejection, the teachings of Wiktor et al regarding culture of the cells on microcarrier beads, scaling up of the cell culture volume, transferring between bioreactors, and eventual inoculation with virus in order to produce the desired viral product from the cells, is equally applicable to MDCK cells as it is to VERO cells.” *Id.* Applicant respectfully disagree.

As discussed above, there are technical difficulties, *e.g.*, homogeneity problems, associated with scaling-up anchorage-dependent cells, *e.g.*, MDCK cells. Griffiths even recognizes these difficulties. See pages 59-60 and 65-66. In addition, other references in the pertinent art, for example, WO 97/37000 to Gröner et al. (“Gröner”), discuss the problems associated with scaling up of anchorage-dependent cells. Gröner at page 3, line 18 to page 4, lines 16. To address these problems, the process in Gröner converts anchorage-dependent cells to cells that grow in suspension to enable better scaling up. See claim 1, page 4, lines 19-24, page 5, lines 18-26, and Example 1. Thus, contrary to the Examiner’s assertions, the teachings regarding culture of the cells on microcarrier beads, scaling up of the cell culture volume, transferring between bioreactors, and eventual inoculation with virus in order to produce the desired viral product from the cells in Wiktor are not equally applicable to MDCK cells as they are to VERO cells.

2. The Examiner failed to establish that Wiktor, Griffiths, and Shimizu teach “a repeated discontinuous” process

In addition, the Examiner acknowledges that Wiktor “differs from the method of the instant claims in that . . . (2) they do not disclose subjecting the ‘preproduction batch’ to a repeated discontinuous process, whereby only a portion of the cells from the preproduction batch are transferred for use in the preparation of the production batch, and the remaining portion of the preproduction batch is transferred for use as a seed for the preparation of at least one subsequent batch.” Office Action at p. 9.

With regard to (2) the repeated discontinuous process, the Examiner asserts that “at the time the invention was made repeated batch cultivation procedures using multiple bioreactors were well known in the art and were recognized as having the

potential to increase overall productivity of a biological product from a cell culture by minimizing overall lag time (i.e., time when no culture is producing biological product)."

Id. The Examiner asserts that "[r]epeated batch cultivation procedures [as disclosed in Shimizu] are considered to be the same as what Applicants are calling a 'repeated discontinuous process.'" *Id.* at pp. 9-10.

According to the Examiner, "[t]he method of Wiktor et al utilizes multiple bioreactors, and thus has the potential to operate on a repeated batch cultivation schedule as taught by Shimizu et al." *Id.* at p. 11. Thus, the Examiner asserts that "one skilled in the art would have been **motivated** to modify the method of Wiktor et al to function on a repeated batch cultivation schedule, using two or more fermentors, in order to eliminate the long period during which scale-up is effected." *Id.* (emphasis added). Further, the Examiner asserts that

One would have had **a reasonable expectation of successfully** modifying the method of Wiktor et al to operate on a repeated batch cultivation schedule because the modification involves the same culture conditions, techniques, and bioreactors as used in the original method of Wiktor et al. The difference in re-seeding of the cultures is clearly taught by Shimizu et al, and is well within the purview of one having ordinary skill in the art.

Id. (emphasis added). Applicants respectfully disagree.

As discussed at page 1 of Applicant's specification, Wiktor describes a method for preparing a large volume of anchorage-dependent cells beginning with a seed population. See Applicant's specification at page 1, lines 15-20. Specifically, Wiktor teaches that the scaling-up of anchorage-dependent cells requires passage of the whole set of microcarrier balls for each scaling-up round. See Wiktor at col. 3, lines 18-

28 and col. 5, lines 14-52. Wiktor teaches that one may successively pass all of the progeny into successively larger bioreactors until an optimum volume is achieved. See *id.* at col. 2, lines 59-67. Indeed, Wiktor teaches that “[a] very important step from the point of view of production on an industrial scale resides in the passage from one biogenerator to another” *Id.* at col. 3, lines 1-3. It is only after several generations of this continuous process that the cells are harvested for their intended use. See *id.* at col. 2, lines 59-67.

Griffiths describes two approaches to scale-up: “The first [approach] is volumetric -- a simple increase in volume while retaining the same cell density or process intensity. See Griffiths at p. 60, lines 3-4. This type of approach is described in Wiktor. The second method described in Griffiths is to increase the cell density/unit vol 10-100-fold by means of medium perfusion techniques.” See *id.* at 4-6. Griffiths further teaches that scaling up “can be achieved by increasing the culture volume, and increasing the microcarrier concentration from the suggested 3-15 g/L.” See *id.* at p. 71, lines 15-17. Thus, the scale-up approaches described in Griffiths teach that the cell culture as a whole, not merely a portion of the cells, is transferred to a larger scale cultivation device.

The teachings of Wiktor are consistent with the teachings of Griffiths. Thus, Wiktor substantiates what is demonstrated by Griffiths, namely that previous methods of scaling-up anchorage-dependent cells involve passaging the whole batch of cells. This is inconsistent with the repeated discontinuous process claimed in independent claims 45 and 64. Hence, Wiktor and Griffith in no way teach or suggest that a repeated

discontinuous (splitting) process as defined in independent claims 45 and 64 could or would be applied to anchorage-dependent cells, *e.g.*, MDCK cells.

The scale-up approaches described in Wiktor and Griffiths teach that the cell culture as a whole, not merely a portion of the cells, is transferred to successively larger biogenerators (parallel production lines) until an optimum volume of cells is achieved. See Wiktor at col. 2, lines 54-68, and at col. 3, lines 1-3. In the final passage, the cells are inoculated for preparing a vaccine. See *id.* In contrast, in the repeated discontinuous process claimed in independent claim 45, the cultured cells are split into two parts, wherein a first part of the cultured cells is transferred to be used for the preparation of at least one production batch (a culture of cells which is employed for the production of at least one virus), and the remaining part of the cultured cells (the second part) is used as a seed for the preparation of at least one subsequent preproduction batch. Neither Wiktor nor Griffiths teach or suggest this type of repeated discontinuous process. Indeed, the Examiner even acknowledges this deficiency in Wiktor and Griffiths. Office Action at pp. 3 and 9 (Griffith et al differs from the instant invention in that . . . they do not explicitly state the harvested cells are split into at least two portions, wherein a first portion of the cells are replated as a seed for a subsequent 'preproduction batch', and a second portion of the cells are transferred and used as a 'production batch' specifically for the production of biological products, which Applicants are calling a 'repeated discontinuous process'; Wiktor et al differs from the method of the instant claims in that . . . they do not disclose subjecting the 'preproduction batch' to a repeated discontinuous process")

As discussed above, the processes disclosed in Wiktor and Griffiths do not involve “dividing” the cells in the manner claimed. Moreover, dividing the cell culture into a first part and a second part is not an inherent aspect of passaging as described in Griffiths. A “passage step” is defined in Applicant’s specification as:

. . . a sequence of activities in the propagation and production of cells comprising at least the transfer of a suitable amount of cells and of a suitable amount of culturing medium into a production vessel, the incubation of the vessel at conditions suitable for the growing a propagation of the cells during a time sufficient for effective growing and propagation of the cells during a time sufficient for effective growing and propagation of the cells.

Applicant’s specification at p. 3, lines 12-16. Based on this definition it is clear that “passaging of cells” involves transferring a number of cells from an existing vessel into a new vessel and is not the same as dividing the cells into two parts as in independent claims 45 and 64.

In the recent appeal in the present application, the Examiner asserted that “Griffiths’ use of the term ‘passaging’ as meaning ‘wherein ‘passaging’ involves splitting the culture and re-seeding and culturing at least one portion of the split culture.’” Decision on Appeal at p. 5. The Board of Patent Appeals and Interferences disagreed with the Examiner’s assertion, stating that “Griffiths did not explicitly explain ‘passaging’ in that way, nor do we see evidence that ‘passaging’ was implicitly intended in that way.” *See id.*

Shimizu does not cure the deficiencies of Wiktor and Griffiths discussed above. Shimizu teaches using multiple fermentors for repeated batch cultivation for non-growth-associated products. However, there is nothing in Shimizu that teaches or suggests

using such a process for anchorage dependent cells, or more specifically MDCK cells. Indeed, Shimizu does not even mention anchorage-dependent or MDCK cells.

Moreover, replating a portion of the cells as a seed for subsequent reproduction batches and transferring a second (larger) portion of cells for use as a production batch for production of biological products produced by the cells (i.e., performing a repeated discontinuous process), is not well-known or routinely performed by one of ordinary skill in the art. As discussed in Section 4 below, because of the technical difficulties, e.g., homogeneity problems, associated with scaling-up anchorage dependent cells, one of ordinary skill in the art would not be prompted to use a repeated discontinuous process to scale up anchorage-dependent cells. Further, one of ordinary skill in the art would not have any reasonable expectation of successfully carrying out a repeated discontinuous process using anchorage-dependent cells because of these homogeneity problems. To the contrary, scaling up of suspension cells is generally considered to be technically much easier and expected to be more reliably suitable for scaling up anchorage-dependent cells, whereas significant technical difficulties would have to be encountered and overcome when performing upscaling for microcarrier cultures. See Section 4 below.

3. The Examiner failed to establish that Wiktor, Griffiths, and Shimizu teach production batches having different passage numbers or teach “the passage number of each production batch is between master cell bank and extended cell bank, and the passage number ensures that the characteristics of the cells obey regulatory restrictions”

Independent claim 45 recites that “the cells of the at least one first production batch in c) have a different passage number than the cells of the at least one

subsequent production batch in e). In addition, claim 45 recites that “the passage number of each production batch is between master cell bank and extended cell bank.” Independent claim 64 includes similar language. None of Wiktor, Griffiths, and Shimizu teach or suggest that a biological may be produced from production batches made according to the claimed invention in which those production batches have different passage numbers. On the contrary, conventional practice shows the production of a biological occurs in production batches all having the same passage number, e.g., serial production. See, e.g., U.S. Patent No. 4,664,912 to Wiktor et al. (“Wiktor”) at col. 2, lines 68-69; see *also* Applicant’s specification at page 1, lines 15-20 and p. 4, lines 26-34. In addition, none of the cited references teach or suggest that the passage number of each production batch is between master cell and extended cell bank. Further, the validation and characterization of the extended cell bank, e.g., as in claims 63 and 76, guarantees that all passage numbers can safely be used for production without any further analytical efforts.

Moreover, Applicant would like to point out that the claim element “the passage number of each production batch is between master cell bank and extended cell bank” does not merely define a time period. In classical serial production, as described in Wiktor and Griffiths, the number of doubling of cells derived from the manufacturers working cell bank at the moment of harvest is known up front within certain limits. See Applicant’s specification at p. 4, lines 15-16. A maximum allowable generation number is set to the production system at the onset. *Id.* at lines 16-17. In contrast, in the claimed method, a bioreactor (manufacturer’s working cell bank) is fed with cells from the master cell bank. The cells from the working cell bank are propagated to a specific

and characterized passage number for an extended cell bank. *See id.* at lines 19-20.

Once the extended cell bank is fully characterized it allows one to produce the biological product with cells at any passage number between master cell bank and extended cell bank since it may be assumed that the cells have not changed. *See id.* at lines 29-32.

As a result, tests on the manufacturer's working cell bank can be limited to sterility testing, which is a particular advantage of the claimed invention. *See id.* at lines 32-33.

4. The Art Teaches Away from the Claimed Invention

There are technical difficulties, e.g., homogeneity problems, associated with scaling-up anchorage-dependent cells. Indeed, Griffiths even recognizes these difficulties. *See* pages 59-60 and 65-66.

In addition, other references in the pertinent art, for example, WO 97/37000 to Gröner et al. ("Gröner"), discuss the problems associated with scaling up of anchorage-dependent cells. Gröner at page 3, line 18 to page 4, lines 16. To address these problems, the process in Gröner converts anchorage-dependent cells to cells that grow in suspension to enable better scaling up. *See* claim 1, page 4, lines 19-24, page 5, lines 18-26, and Example 1.

The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is "strong evidence of unobviousness." *In re Hedges*, 783 F.2d 1038, 1041, 228 U.S.P.Q. 685, 687 (Fed. Cir. 1986). Furthermore, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." *United States v. Adams*, 383 U.S. 39, 52, 148 U.S.P.Q. 479, 484 (1984). As discussed above, Gröner discourages scaling-up of anchorage-dependent cell systems for the production of a

biological. Considering the drawbacks associated with scaling up anchorage-dependent cells, it would be unlikely for one of ordinary skill in the art to use anchorage-dependent cells when devising a scaled-up preparation of cells for use in the production of biologicals. Thus, the art teaches away from the claimed invention.

The disclosure of a reference must be considered in its entirety, i.e., as a whole. See M.P.E.P. § 2141.02(V). Cited art will teach away when it teaches or suggests that the developments flowing from its disclosures are unlikely to produce the objective of Applicant's invention. See *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Here, the cited reference, Griffiths, as well as the prior art, Gröner, teach away from scaling-up of anchorage-dependent cell systems comprising a repeated discontinuous process as defined in claim 45. As discussed above, Griffiths discusses the difficulties, e.g., homogeneity problems, associated with scaling up of anchorage-dependent cells. See Griffiths at pp. 59-60 and 65-66. To address these problems, Gröner converts anchorage-dependent cells to cells that grow in suspension to enable better scaling up. See Gröner claim 1, p. 3, lines 18 to p. 4, line 12, p. 4, lines 19-24, p. 5, lines 18-26, and Example 1. Gröner teaches that this process provides a simple and economical manner of replicating influenza viruses in cell cultures of adherently growing cells (anchorage-dependent cells). See *id.* at p. 4, lines 21-24. Thus, based on the teachings of Gröner, it would be unlikely for one of ordinary skill in the art to devise a scaled-up preparation of cells for use in the production of a virus using unaltered anchorage-dependent cells rather than anchorage-dependent cells that are adapted to grow in suspension.

5. Shimizu does not Cure the Deficiencies of Wiktor and Griffiths

Shimizu does not cure the deficiencies of Wiktor and Griffiths discussed above. Shimizu teaches using multiple fermentors for repeated batch cultivation for non-growth-associated products. However, there is nothing in Shimizu that teaches or suggests using such a process for anchorage dependent cells, *e.g.*, MDCK cells. Indeed, Shimizu does not even mention anchorage-dependent cells or MDCK cells. Thus, there is no reason why one of ordinary skill in the art would have combined the processes of Wiktor, Griffiths, and Shimizu with any reasonable expectation of success, and without the benefit of hindsight, which is impermissible. See M.P.E.P. § 2142.

Moreover, as discussed above, Griffiths and Gröner teach away from the claimed invention, *i.e.*, a method for the preparation of cells for use in the production of a virus using unaltered anchorage dependent cells. Thus, one of ordinary skill in the art would have been led away from modifying Wiktor as suggested by the Examiner.

Further, there is nothing in Shimizu that teaches or suggests a scale-up process for producing a virus using MDCK cells. Rather, Shimizu discloses the use of repeated batch cultivation for non-growth-associated products such as L-glutamic acid and penicillin. See Shimizu at p. 743. Indeed, Shimizu does not even mention anchorage-dependent cells. Thus, there is no reason why one of ordinary skill in the art would have combined the processes of Wiktor, Griffiths, and Shimizu. Moreover, given the homogeneity problems associated with scaling-up anchorage dependent cells, see Griffiths at pp. 65-66 and Gröner at p. 4, lines 18-38, there is no reasonable expectation that using the repeated batch cultivation process of Shimizu with anchorage-dependent

cells would be successful. In fact, one would expect that using anchorage-dependent cells in the repeated batch cultivation process of Shimizu would not be successful as it would still require opening individual cell culture vessels several times, e.g., opening the vessels for each transfer step and for adding fresh medium, which would result in contamination of the cell culture.

6. Applicant's Claimed Method Produces Unexpected Results

To further show that the claimed methods are patentable, Applicant points to the unexpected results of the presently claimed invention. In particular, "[t]he method described allows high through-put production since the up scaling route from WCS to production cells can be very much shortened and much less bioreactors are needed since parallel production lines are not needed anymore." Specification, page 3, line 35 to page 4, line 2. In contrast to prior art methods, such as that described in Wiktor, this can represent a significant savings in time, resource allocation, and money, resulting in smaller and better-controlled growth and harvesting processes, particularly for viruses. Applicant submits that the claimed method thus results in an unexpectedly facile method for the production of viruses. Accordingly, this evidence is relevant to the issue of obviousness and must be considered. M.P.E.P. 2141(II).

7. The proportion of cell culture to be transferred in each step is not a result effective variable

The Examiner admits that "the modified method of Wiktor et al still differs from the method of instant claim 48 in that there are no teaching in Shimizu et al as to the specific proportion of the cell culture to be transferred in each step." Office Action at p. 14. The Examiner, however, asserts that "the difference between the proportions of

the total cell culture allotted for production of biological product and for use as a subsequent preproduction batch would have been routinely optimized by one having ordinary skill in the art.” *Id.* Applicants respectfully disagree.

According to *In re Aller*, it would be obvious to optimize general conditions of a claim that are disclosed in the prior art. See 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). However, Wiktor and Shimizu fail to teach or suggest all the elements of Applicant’s claim 48, which the Examiner admits. See Office Action at p. 14 (“The modified method of Wiktor et al still differs from the method of instant claim 48 in that there are no teachings in Shimizu et al as to the specific proportion of the cell culture to be transferred in each step”). Thus, modifying the proportions of cells disclosed in Wiktor and Shimizu especially the proportions of the cells used for at least one production batch and the cells used for at least one subsequent preproduction batch, cannot justifiably be considered merely determining optimum or workable ranges as in *In re Aller*.

Accordingly, for at least the foregoing reasons, the Examiner failed to establish a *prima facie* case of obviousness over Wiktor, Griffiths, and Shimizu.

III. DOUBLE PATENTING

Claims 45-76 are provisionally rejected for obviousness-type double patenting as allegedly unpatentable over claims 26-30, 32-34, 35-39, and 42-45 of co-pending Application No. 11/654,556. Office Action at p. 17.

While Applicant respectfully submits that the present invention is not obvious over any claim of the cited application, solely to expedite allowance of the present application, Applicant presently plans to file a terminal disclaimer to overcome this

rejection. However, because the rejection is based on a currently co-pending application, Applicant will wait to receive a Notice of Allowance in this or the co-pending case. At such time, Applicant will then review the claims in both applications to determine if the present plan is still appropriate.

IV. CONCLUSION

In view of the foregoing remarks, Applicant respectfully requests reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: September 23, 2011

By: Jennifer R. Gupta
Jennifer R. Gupta
Reg. No. 54,257